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December 21, 1999

ATTN: BOX PCT
Assistant Commissioner for Patents
Washington, D.C. 20231

ATTN: BOX PCT

Re: Application of Yoshihisa NISHIBE, Wataru KINOSHITA and Hiroyuki KAWABE
PHARMACEUTICAL COMPOSITION FOR APPLICATION TO MUCOSA
Our Reference: Q57234
PCT/JP99/02126, filed April 21, 1999

Dear Sir:

Applicants herewith submit the attached papers for the purpose of entering the National stage under 35 U.S.C. § 371 and in accordance with Chapter I of the Patent Cooperation Treaty. Attached hereto is the application identified above which is a translation of PCT International Application No. **PCT/JP99/02126, filed April 21, 1999**, comprising the specification, claims, four (4) sheets of drawings, executed Declaration and Power of Attorney, English translation of Article 19 Amendments, Information Disclosure Statement, PTO Form 1449 with references, International Search Report, executed Assignment and PTO Form 1595.

The Government filing fee, after consideration of Article 19 Amendments, is calculated as follows:

Total Claims	33 - 20 =	13 x $18 =	$ 234.00
Independent Claims	2 - 3 =	0 x $78 =	$ 000.00
Base Filing Fee	($840.00)		$ 840.00
Multiple Dep. Claim Fee	($260.00)		$ 260.00
TOTAL FILING FEE			**$ 1,334.00**
Recordation of Assignment Fee			$ 40.00
TOTAL U.S. GOVERNMENT FEE			**$ 1,374.00**

Checks for the statutory filing fee of **$ 1,334.00** and Assignment recordation fee of **$ 40.00** are attached. You are also directed and authorized to charge or credit any difference or overpayment to Deposit Account No. 19-4880. The Commissioner is hereby authorized to charge any fees under 37 C.F.R. 1.492; 1.16 and 1.17 which may be required during the entire pendency of the application to Deposit Account No. 19-4880. A duplicate copy of this transmittal letter is attached.

Priority is claimed from:

Japanese Patent Application	Filing Date
10-110887 (Pat.Appln.)	April 21, 1998
10-110888 (Pat.Appln.)	April 21, 1998

The Office is invited to contact the above firm on any question which might arise on the above-named application. Any contact that the Office might need to make should be directed to the undersigned at (202)293-7060.

Respectfully submitted,
SUGHRUE, MION, ZINN, MACPEAK & SEAS
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By _____
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TO THE INTERNATIONAL BUREAU OF THE WORLD
INTERNATIONAL PROPERTY ORGANIZATION
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"Amendment of the claims under Article 19(1)(Rule 46)"

International Application No. PCT/JP99/02126
(Our Ref.: G836-PCT)

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The applicant requests amendment of the claims of the present international application, based on Article 19, of the PCT, and transmits herewith newly amended claims. We believe the amendment does not go beyond the disclosure in the original international application.

An outline of the amendment is as follows.

1. Original claim 2 is cancelled.

2. Original claims 17, 23 and 25 to 29 are amended.

3. Other claims are maintained without change.

The applicant also files the attached brief statement which explains the amendment, and indicates any impact that the amendments therein might have on the description.

Explanation according to Article 12(1) of PCT

The claims described in the replaced papers relate to the original claims as follows.

(1) Claim 2 is cancelled.

(2) In claim 17, "claims 1 to 16" is amended to --claims 1 or 3 to 16--.

(3) In claim 23, "claims 1 to 22" is amended to --claims 1 or 3 to 22--.

(4) In claim 25, "claims 1 to 24" is amended to --claims 1 or 3 to 24--.

(5) In claim 26, "claims 1 to 24" is amended to --claims 1 or 3 to 24--.

(6) In claim 27, "claims 1 to 26" is amended to --claims 1 or 3 to 26--.

(7) In claim 28, "claims 2 to 27" is amended to --claims 3 to 27--.

(8) In claim 29, "claims 2 to 28" is amended to --claims 3 to 28--.

DESCRIPTION

PHARMACEUTICAL COMPOSITION FOR APPLICATION TO MUCOSA

Technical Field

The present invention relates to a pharmaceutical composition for application to the mucosa to be used in drug therapy comprising a water-insoluble and/or water-low soluble substance, a medicament, and an aqueous medium, and having an osmotic pressure of less than 290 mOsm. More specifically, the present invention relates to a pharmaceutical composition for application to the mucosa comprising a water-insoluble and/or water-low soluble substance, a medicament, and an aqueous medium, and having an osmotic pressure of less than 290 mOsm, that is superior to conventional pharmaceutical compositions for application to the mucosa, due to efficient and high permeability to the blood at the mucosa.

The present invention also relates to a pharmaceutical composition for application to the mucosa comprising a hemostatic agent and a medicament. More specifically, the present invention relates to a pharmaceutical composition for application to the mucosa in which a medicament has been mixed with a hemostatic agent and that is superior over conventional pharmaceutical compositions for application to the mucosa due to high permeability and retention at the mucosa.

Background Art

Application to the mucosa as a method of drug therapy has been recognized as a useful means of medication for such reasons as (1) it permits direct application to the affected area for diseases of local areas such as nasal mucosa, oral mucosa, and vaginal mucosa, (2) its immediate effects for systemic diseases can be expected as in the case of a nasal spray to the nasal mucosa and a suppository to the rectal mucosa, and

(3) its application is easy compared to injection, as represented by an oral drug targeted at the intestinal mucosa, and the like. For example, pharmaceutical preparations for application to the mucosa have already been commercially available due to reason (1) in the case of nasal sprays for treatment of allergic rhinitis, and due to reason (2) in the case of suppositories to alleviate pain.

As pharmaceutical preparations for local mucus diseases, Saunders et al., (WO 92-14473), for example, provides a suspension preparation containing Tipredane as the main drug as the pharmaceutical preparation for treatment of allergic rhinitis. Also, Helzner (WO 97-01337) provides a pharmaceutical preparation comprising an antihistamic drug, a steroid and water as the pharmaceutical preparation for treatment of allergic rhinitis. As the pharmaceutical preparation for local mucus diseases, furthermore, Kim et al., (WO 98-00178) provides a suspension preparation having a thixotropic property as the pharmaceutical preparation for application to the nasal mucosa. Suzuki et al. (Japanese Examined Patent Publication (Kokoku) No. 60 (1985)-34925) also provides a sustained release pharmaceutical preparation for administration to the nasal cavity that permits the efficient supply of the drug at a concentration sufficient to obtain a therapeutic effect.

As the pharmaceutical preparations for systemic diseases, several methods have been provided that enhance the absorption of drugs through the mucosa. Nagata et al. (Japanese Unexamined Patent Publication (Kokai) No. 63 (1988)-303931), for example, provides a method of applying to the nasal cavity a growth hormone-releasing factor at the liquid form having an osmotic pressure ratio of 1 (an osmotic pressure of 290 mOsm) or lower as a method for enabling quick and efficient absorption of the a growth hormone-releasing factor through the nasal mucosa to the blood circulation. Furthermore, Ohwaki et

al. (Japanese Unexamined Patent Publication (Kokai) No. 60 (1985)-123426) provides a method of applying to the nasal cavity a solution of secretin having an osmotic pressure ratio of 1 to 5 (an osmotic pressure of 290-1450 mOsm) and a pH of 2 to 5 as a method for enabling quick absorption of secretin through the nasal mucosa to blood circulation. Furthermore, Awatsu et al. (Pharm. Res. Vol. 10, No. 9, 1372-1377, 1993) provides a method of applying to the nasal mucosa a pharmaceutical solution to which polyoxyethylene 9-laurylether was added as an absorption enhancer as a method for enabling efficient absorption of a granulocyte colony-stimulating factor through the nasal mucosa to blood circulation.

However, when these pharmaceutical preparations are given to the mucosa, liquid-dripping can occur, or the pharmaceutical preparations are quickly excreted to the outside of the mucus tissue due to a mucociliary clearance function etc. before being adequately transported or permeated to the mucosa tissue. Because of this, the transport of an adequate amount of drug into the blood cannot be effected when systemic administration through transport to the blood circulation is attempted. Furthermore, the method of using an absorption enhancer is yet to be realized because the absorption enhancer has the problem of irritating the nasal mucosa. On the other hand, when local administration is attempted through retention of the drug in the mucosa tissue, an adequate amount of the drug cannot be retained at the tissue. In addition, even if the problem of retentivity has been solved, permeation into the mucosa tissue is not adequate.

Thus, it is strongly desired to develop a pharmaceutical preparation for application to the mucosa, that allows the transport of an adequate amount of the drug through the mucosa to the blood circulation after the application to the mucosa. Alternatively, it is strongly desired to develop a pharmaceutical preparation

for application to the mucosa that enables the transport to and retention in the mucosa tissue of an adequate amount of the drug when applied to the mucosa.

Disclosure of the Invention

Thus, the first object of the present invention is to provide a pharmaceutical composition for application to the mucosa, that has efficient and high permeability through the mucosa to the blood when applied to the mucosa.

The second object of the present invention is to provide a pharmaceutical composition for application to the mucosa, that has efficient and high permeability to the mucosa and retentivity at the mucosa when applied to the mucosa.

After intensive studies to attain the above first object, the present inventors have found that it is possible to provide a pharmaceutical preparation for application to the mucosa that is superior over conventional liquid composition due to efficient and high permeability through the mucosa to the blood, by formulating a drug that contains a water-insoluble and/or water-low soluble substance and that has an osmotic pressure of less than 290 mOsm, and thereby have reached the present invention.

An enhanced absorption of a drug through the mucosa by controlling the osmotic pressure of a pharmaceutical preparation is disclosed in a patent to Ohwaki and has been reported in a paper by Awazu et al. (Pharm. Res. Vol. 10, No. 9, 1372-1377, 1993). However, these phenomena are only observed in aqueous solution preparations that do not contain a water-insoluble and/or water-low soluble substance, and thereby are essentially different from the pharmaceutical preparation of the present invention in which the inclusion of a water-insoluble and/or water-low soluble substance is essential. Furthermore, it has been shown in Osada's

patent that absorption through the rat nasal mucosa of growth hormone releasing factor is higher when the preparation has an osmotic pressure ratio of 1 (osmotic pressure of 290 mOsm) or lower, and in Ohwaki's patent it is higher when secretin has an osmotic pressure ratio of 1 (osmotic pressure of 290 mOsm) or greater, and in Awazu's patent the absorption of granulocyte colony-stimulating factor is higher when the preparation has an osmotic pressure of 285 mOsm than 174 mOsm. These observations thereby suggest that it is not easy to think of the present invention that permits enhanced absorption regardless of the type of drug used. In these aqueous solution preparations the degree of enhancement in absorption by controlling osmotic pressure is at most about 3-fold compared to the isotonic pharmaceutical preparations, and therefore the degree of 10 to 20-fold of the present invention is surprising.

The patent application by Saunders (WO 92-14473) and Helzner (WO 97-01337) described above describe pharmaceutical preparations containing a water-insoluble and/or water-low soluble substance. However, Saunders' patent application (WO 92-11473) makes no description of osmotic pressure of pharmaceutical preparations in general, in its claim, and merely describes in the specification that isotonicity is preferred, and Helzner's patent application makes no description of osmotic pressure of pharmaceutical preparations in general, and merely describes in the specification that the addition of an isotonic agent is preferred. From these patents, therefore, one cannot expect a drastic enhancement in the absorption at low osmotic pressures.

It is surprising therefore that the effect of enhancing drug absorption through the mucosa is drastic when a water-insoluble or water-low soluble substance is coexistent. That is, although there are reports that the effect of low osmotic pressure is observed in some aqueous solution preparations, we have found,

surprisingly, that the effect can be observed by adding a water-insoluble or water-low soluble substance and the effect does not depend on the type of the drug used.

Thus, in the first aspect, the present invention provides an aqueous pharmaceutical composition for application to the mucosa comprising one or more water-insoluble substance and/or water-low soluble substance and one or more medicament, and having an osmotic pressure of less than 290 mOsm. The composition is a pharmaceutical composition for application to the mucosa that is superior over conventional pharmaceutical compositions for application to the mucosa, due to markedly efficient and high permeability to the blood at the mucosa.

After intensive studies to attain the above second object, the present inventors have found that by formulating a pharmaceutical preparation in which a hemostatic agent has been added to a pharmaceutical preparation containing a medicament, a pharmaceutical composition for application to the mucosa having efficient and high permeability to and retentivity at the mucosa can be provided, and thereby have attained the present invention.

Thus, in the second aspect, the present invention provides a pharmaceutical composition for application to the mucosa comprising one or more hemostatic agent and one or more medicament, and more specifically, an aqueous pharmaceutical composition for application to the mucosa comprising one or more hemostatic agent, one or more water-insoluble substance and/or water-low soluble substance and one or more medicament, and having an osmotic pressure of less than 290 mOsm. The composition is a pharmaceutical composition for application to the mucosa, that is superior over conventional pharmaceutical compositions for application to the mucosa, due to markedly efficient and high permeability and retentivity at the mucosa.

Brief Description of Drawings

Figure 1 is a graph showing the relationship between osmotic pressure and bioavailability in the result that compares the absorptivity of fluorescein in Working example 1 and Comparative example 1.

Figure 2 is a graph showing the relationship between osmotic pressure and bioavailability in the result that compares the absorptivity of 5-carboxy fluorescein in Working example 2 and Comparative example 2.

Figure 3 is a graph showing the relationship between osmotic pressure and bioavailability in the result that compares the absorptivity of salmon calcitonin in Working example 3 and Comparative example 3.

Figure 4 is a photograph showing the expansion of the composition when the composition of the present invention having an osmotic pressure of 10 mOsm (A) or a composition having an osmotic pressure of 290 mOsm (isotonic pressure) was added to a physiological saline having the same osmotic pressure as the mucus (thereby simulating the mucus) on the mucosa.

Embodiments for Carrying out the Invention

As the medicament of the present invention, any agent can be applied including, for example, one for sedative hypnotics, one for antianxiety drugs, one for anticonvulsants, one for analgesic antipyretics, one for local anesthetics, one for antispasmodics, one for cardiac stimulants, one for diuretics, one for vasoconstrictors, one for vasodilators, one for bronchodilators, one for peptic ulcer drugs, one for analgesics, one for hormone preparations, one for antidotes, one for vaccines, one for antibiotics, one for chemotherapeutics, one for anti-Parkinson drugs, one for psychoneurotics, one for muscle relaxants, one for antiarrhythmic drugs, one for antihypertensive drugs, one for hypolipidemic drugs, one for respiratory stimulants,

one for expectorants, one for antiflatuents, one for vitamins, one for antiallergic drugs, and the like. Among them, relatively liposoluble agents are preferred and specific examples include liposoluble vitamins, steroids, and prostaglandins. Among the highly water-soluble agents, those having a high molecular weight are preferred, and specific examples include proteins, and peptides.

Agents that develop beneficial effects when present in the mucosa include, for example, antiallergic drugs such as tranilast, amlexanox, repirinast, ibudilast, tazanolast, pemirolast, oxatomide, azelastine hydrochloride, terfenadine, astemizole, sodium cromoglicate, ketotifen fumarate, emedastine fumarate, epinastine hydrochloride, mequitazine, suplatast tosilate, ozagrel, seratorodast, pranlukast, 5-lipoxygenase inhibitors, and platelet activating antagonists; steroids for rhinitis and asthma such as beclometasone dipropionate, fluticasone propionate, flunisolide, and mometasone; vaccines such as influenza HA vaccine, and; agents for genetic therapy such as antisense, ribozyme, and vectors.

In the first aspect of the present invention, the water-insoluble and/or water-low soluble substance is an essential component, and in the second aspect of the present invention, the composition preferably contains a water-insoluble and/or water-low soluble substance. Such a water-insoluble or water-low soluble substance may be any substance, and preferred examples include celluloses and more preferably crystalline celluloses.

The concentration of the water-insoluble and/or water-low soluble substance, that is present as solid particles in an aqueous medium in the first aspect of the present invention, is preferably 0.1% w/w or greater relative to the total amount of the preparation, and more preferably 1% to 10% w/w. The concentration of the water-insoluble and/or water-low soluble substance that

is present as solid particles in an aqueous medium in the second aspect of the present invention is preferably 0.1% w/w or greater relative to the total amount of the preparation, and more preferably 1% to 10% w/w.

In any of the aspects of the present invention, preferably the water-insoluble or water-low soluble substance that is present as solid particles in an aqueous medium is homogeneously dispersed in the aqueous medium.

In any of the aspects of the present invention, preferably a water-soluble polymer is further added to the composition. Specifically, alginic acid, propylene glycol, polyethylene glycol, glycerin, polyoxyethylene polyoxypropylene glycol, pectin, low methoxyl pectin, guar gum, gum arabic, carrageenan, methyl cellulose, carboxymethyl cellulose sodium, xanthan gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, and the like can be mentioned, and preferably carboxymethyl cellulose sodium, xanthan gum, and hydroxypropyl cellulose can be mentioned. The above polyoxyethylene polyoxypropylene glycol is a series of polymers in which ethylene oxide has been addition-polymerized to a polypropylene glycol obtained by polymerization of propylene oxide, and are classified into several types by the difference in the mean degree of polymerization of propylene oxide and ethylene oxide, with any type being usable in the present invention. In addition, as preferred combinations of a water-soluble polymers and water-insoluble and/or water-low soluble substance, there can be mentioned crystalline cellulose carmellose sodium that is a mixture of carboxymethyl cellulose sodium and crystalline cellulose. Preferably the concentration of these water-soluble polymers, when added, is 1% w/w to 30% w/w relative to the water-insoluble and/or water-low soluble substance.

It is an essential requirement in the first aspect of the present invention that the osmotic pressure of the

pharmaceutical preparation is less than 290 mOsm, and preferably it is 150 mOsm or lower, more preferably 60 mOsm or lower, more preferably 30 mOsm or lower, and most preferably 10 mOsm or lower. The control of osmotic pressure is not required in the second aspect of the present invention, but it is preferably lower than the osmotic pressure of the mucus at the mucosa of the targeted administration site, and specifically it is less than 290 mOsm, preferably 150 mOsm or lower, more preferably 60 mOsm or lower, more preferably 30 mOsm or lower, and most preferably 10 mOsm or lower.

In the present invention, the addition of a substance for controlling osmotic pressure (osmotic pressure-controlling agent) is not particularly required, but when it is added any substance can be used. Specific examples include salts such as sodium chloride, and water-soluble sugars such as glucose, and among them salts such as sodium chloride are preferred.

The hemostatic agent for use in the second aspect of the present invention may be any agent, and specific examples include tranexamic acid, epsilon aminocaproic acid, carbazochrome, carbazochrome sulfonate, carbazochrome sodium sulfonate, phytonadione, etamsylate, monoethanol amine oleate, thrombin, hemocoaglase, adrenochrome monoaminoguanidine mesilate, and the like. When the above water-soluble polymer is added, the hemostatic agent or the medicament is preferably highly liposoluble, and specific examples include carbazochrome, carbazochrome sulfonate, and carbazochrome sodium sulfonate as the hemostatic agent, and liposoluble vitamins, steroids, and prostaglandins as the medicament. As the highly water-soluble medicament, a high molecular weight compound is preferred and specific examples include proteins and peptides.

In the present invention, a known surfactant can be added and specific examples include polysorbate 80, glycerin monostearate, polyoxyl stearate, Lauromacrogol,

sorbitan oleate, sucrose fatty acid esters, and the like. Among them, polysorbate 80 is most preferred.

The amount of the medicament for use in the present invention is a therapeutically effective amount and can be determined depending on the type of drug administered, the type and the degree of the disease, the age and the weight of the patient, and the like. It is usually from the same to 20 times as much as the amount of each drug commonly used for injection, more preferably from the same to 10 times as much.

The concentration of the medicament of the present invention is preferably 0.01% w/w to 1% w/w relative to the total amount of the pharmaceutical preparation, and most preferably 0.05% w/w to 0.5% w/w.

In order to improve the physical properties, appearances, or smells of the composition of the present invention, a known antiseptic, a pH controlling agent, a preservative, a buffer, a colorant, a smell corrigent, and the like may be added, as desired. For example, benzalkonium chloride as the antiseptic, hydrochloric acid as the pH controlling agent, ascorbic acid as the preservative, citric acid and salts thereof as the buffer, Red No. 2 as the colorant, menthol as the smell corrigent may be mentioned.

The mucosa to which the present invention is applied may be any mucosa. Specific examples include intestinal mucosa, gastric mucosa, nasal mucosa, tracheal/bronchial/pulmonary mucosa, mucosa of oral cavity, rectal mucosa, vaginal mucosa, and the like, and nasal mucosa is most preferred.

The composition of the present invention may be formulated in a dosage form suitable for administration as a pharmaceutical preparation. It may contain an indirect dosage form such as an oral formulation for administration to the gastric and intestinal mucosa, but the composition of the present invention is preferably administered directly to the mucosa, and most preferably

it takes a dosage form that can be sprayed as a mist. In this case, the composition of the present invention may be filled in a gastric or enteric capsule, for example, and the composition is exposed at the desired site of mucosa. As another dosage form, when given to the rectal mucosa, the present invention may be filled in a capsule in a unit dosage form, which is administered as a suppository. When given to the oral mucosa, nasal mucosa, or vaginal mucosa, the composition of the present invention may be filled in a spray-type container, a fixed amount of which is sprayed to the oral cavity, nose, or vagina. When given to the tracheal/bronchial/pulmonary mucosa, the present invention may be filled to an inhalation-type container, which is allowed to be inhaled into the trachea, bronchus, or lung.

EXAMPLES

The present invention will now be explained with reference to the following examples.

Fluorescein and carboxy fluorescein used in the present invention are substances generally used as a model drug of the liposoluble low molecular weight drug and of the water-soluble low molecular weight drug, respectively. As an example of the water-soluble high molecular weight drug, salmon calcitonin was used. Fluorescein was obtained from Wako Pure Chemicals, 5-carboxy fluorescein was from Molecular Probes, salmon calcitonin was from Bachem, crystalline cellulose carmellose sodium was from Aviel™ RC-591NF manufactured by Asahi Chemical Industry, Co., Ltd., Polysorbate 80 was from Wako Pure Chemicals, benzalkonium chloride was from Nakalai Tesque, glucose was from Wako Pure Chemicals, sodium chloride was from Wako Pure Chemicals, caroboxymethyl cellulose sodium was from Wako Pure Chemicals, carbazochrome was from Wako Pure Chemicals, tranexamic acid was from Wako Pure Chemicals.

Example 1.

Fluorescein composition Nos. 1 to 10 for application to the mucosa comprising the components described in the following Table 1 were prepared. For each pharmaceutical preparation, osmotic pressure was measured using the Micro-Osmometer Model 3MO from Advance Instruments, Inc. The result is shown in Table 1.

One hundred μl each of the compositions 1 to 10 for application to the nasal mucosa was sprayed to the unilateral nasal cavity of rabbits (Japanese White, male, weighing 3 kg) using a commercially available suspension device. At 5, 10, 15, 30, 60, and 120 minutes after the administration, 0.5 ml of the blood was taken from the ear vein and the plasma level of fluorescein was determined by HPLC. From the time-concentration curve till 120 minutes after the spraying, $AUC_{0-120min}$ was determined and bioavailability (B.A.) for the intravenous injection was calculated. The mean values of three rabbits are shown in Table 1.

Table 1

Composition No.	Composition	Osmotic pressure (mOsm)	B.A. (%)
1	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w	5	63
2	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Sodium chloride: 0.08% w/w	30	47
3	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Sodium chloride: 0.2% w/w	72	16
4	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Sodium chloride: 0.4% w/w	128	13
5	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Glucose: 0.5% w/w	30	29
6	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Glucose: 1.2% w/w	72	10
7	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Glucose: 2.1% w/w	128	9
8	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 0.1% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w	0	22
9	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 0.5% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w	0	37
10	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 3.0% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w	7	53

Comparative example 1.

Fluorescein composition Nos. 11 to 16 for application to the mucosa comprising the components described in the following Table 2 were prepared. For each pharmaceutical preparation, osmotic pressure was measured using the Micro-Osmometer Model 3MO from Advance Instruments, Inc. The result is shown in Table 2. Bioavailability (B.A.) of the compositions 11 to 16 determined by the method described in Working example 1 is also shown in Table 2.

Table 2

Composition No.	Composition	Osmotic pressure (mOsm)	B.A. (%)
11	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Sodium chloride: 0.9% w/w	290	7
12	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Glucose: 5% w/w	340	7
13	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Glucose: 67% w/w	4000	4
14	Fluorescein: 0.1% w/w Carboxy methyl cellulose sodium: 0.2% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w	5	7
15	Fluorescein: 0.1% w/w Carboxy methyl cellulose sodium: 0.2% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Sodium chloride: 0.08% w/w	30	5
16	Fluorescein: 0.1% w/w Carboxy methyl cellulose sodium: 0.2% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Glucose: 0.5% w/w	30	5

Example 2.

5-Carboxy fluorescein composition Nos. 17 to 18 for application to the mucosa comprising the components described in the following Table 3 were prepared. For each pharmaceutical preparation, osmotic pressure was measured using the Micro-Osmometer Model 3MO from Advance Instruments, Inc. The result is shown in Table 3. Bioavailability (B.A.) of the compositions 17 to 18 determined by the method described in Working example 1

is also shown in Table 3.

Table 3

Composition No.	Composition	Osmotic pressure (mOsm)	B.A. (%)
17	5-carboxy fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w	6	52
18	5-carboxy fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Glucose: 0.4% w/w	30	47

Comparative example 2.

5-Carboxy fluorescein composition Nos. 19 to 22 for application to the mucosa comprising the components described in the following Table 4 were prepared. For each pharmaceutical preparation, osmotic pressure was measured using the Micro-Osmometer Model 3MO from Advance Instruments, Inc. The result is shown in Table 4. Bioavailability (B.A.) of the compositions 19 to 22 determined by the method described in Working example 1 is also shown in Table 4.

Table 4

Composition No.	Composition	Osmotic pressure (mOsm)	B.A. (%)
19	5-carboxy fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Glucose: 5% w/w	340	5
20	5-carboxy fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Glucose: 67% w/w	4000	3
21	5-carboxy fluorescein: 0.1% w/w Carboxy methyl cellulose sodium: 0.2% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w	6	7
22	5-carboxy fluorescein: 0.1% w/w Carboxy methyl cellulose sodium: 0.2% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Glucose: 0.4% w/w	30	3

Example 3.

Salmon calcitonin composition Nos. 23 to 24 for application to the mucosa comprising the components described in the following Table 5 were prepared. For each pharmaceutical preparation, osmotic pressure was measured using the Micro-Osmometer Model 3MO from Advance Instruments, Inc. The result is shown in Table 5. Bioavailability (B.A.) of the compositions 23 to 24 determined by the method described in Working example 1 is also shown in Table 5.

Table 5

Composition No.	Composition	Osmotic pressure (mOsm)	B.A. (%)
23	Salmon calcitonin: 0.008% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w	10	52
24	Salmon calcitonin: 0.008% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Glucose: 0.4% w/w	30	47

Comparative example 3.

Salmon calcitonin composition Nos. 25 to 28 for application to the mucosa comprising the components described in the following Table 6 were prepared. For each pharmaceutical preparation, osmotic pressure was measured using the Micro-Osmometer Model 3MO from Advance Instruments, Inc. The result is shown in Table 6. Bioavailability (B.A.) of the compositions 25 to 28 determined by the method described in Working example 1 is also shown in Table 6.

Table 6

Composition No.	Composition	Osmotic pressure (mOsm)	B.A. (%)
25	Salmon calcitonin: 0.008% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Glucose: 5% w/w	340	3
26	Salmon calcitonin: 0.008% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Glucose: 67% w/w	4000	2
27	Salmon calcitonin: 0.008% w/w Caroboxymethyl cellulose sodium: 0.2% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w	6	5
28	Salmon calcitonin: 0.008% w/w Caroboxymethyl cellulose sodium: 0.2% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Glucose: 0.4% w/w	30	5

When the model drug is a liposoluble low molecular weight substance, fluorescein, plasma levels of fluorescein in rabbits that were sprayed with a pharmaceutical preparation having a low osmotic pressure of 5 mOsm (Composition No. 1) to the nasal mucosa were markedly higher than those in rabbits that were sprayed with a pharmaceutical preparation having an almost isotonic osmotic pressure of 340 mOsm (Composition Nos. 11 and 12) or with a pharmaceutical preparation having a high osmotic pressure of 4000 mOsm (Composition No. 13), and, as shown in Table 1, the bioavailability is increased by 8 to 15 fold. Bioavailability decreases with increased osmotic pressure, and at 30 mOsm (Composition No. 2) it is three-fourth that of 5 mOsm (Composition No. 1) and at a higher 72 mOsm (Composition No. 3) it decreases to a great extent. Even at 128 mOsm (Composition No. 4) it exhibits a bioavailability about

twice as high as that of the pharmaceutical preparation having 290 mOsm or greater (Composition Nos. 11 to 13). It has been also shown that even when isotonic at low osmotic pressure, salts such as sodium chloride (Composition Nos. 2 to 4) have higher bioavailability than water-soluble salts such as glucose (Composition Nos. 5 to 7). Furthermore, it indicates that up to about 1.5%, the higher the concentration of the water-insoluble or water-low soluble substances is, the higher the bioavailability is (comparison between Composition Nos. 8 and 9 and Composition No.1). Even for the pharmaceutical preparations having a low osmotic pressure, plasma levels were almost equal to the pharmaceutical preparations having isotonic or high osmotic pressure when they do not contain water-insoluble or water-low soluble substances (Composition Nos. 14 to 16). These results indicate that the effect of osmotic pressure of the pharmaceutical preparation which is isotonic or lower on the permeability of the water-low soluble substance to the blood at the mucosa is markedly exhibited only when a water-insoluble or water-low soluble substance is included, and thereby the effect of the aqueous pharmaceutical composition of the present invention for application to the mucosa was demonstrated.

When the model drug is a water-soluble low molecular weight substance, 5-carboxy fluorescein, plasma levels of 5-carboxy fluorescein in rabbits that were sprayed with a pharmaceutical preparation having a low osmotic pressure of 6 mOsm (Composition No. 17) to the nasal mucosa were markedly higher than those in rabbits that were sprayed with a pharmaceutical preparation having an almost isotonic osmotic pressure of 340 mOsm (Composition Nos. 19) or with a pharmaceutical preparation having a high osmotic pressure of 4000 mOsm (Composition No. 20), and, as shown in Table 3, the bioavailability is increased by 9 to 17 fold. Furthermore, even for the pharmaceutical preparations having a low osmotic pressure, plasma levels

were almost equal to the pharmaceutical preparations having isotonic or high osmotic pressure when they do not contain a water-insoluble or water-low soluble substance (Composition Nos. 21 to 22).

These results indicate that the effect of osmotic pressure of the pharmaceutical preparation which is isotonic or lower on the permeability of the water-low soluble substance to the blood at the mucosa is markedly exhibited only when a water-insoluble or water-low soluble substance is included, and thereby the effect of the aqueous pharmaceutical composition of the present invention for application to the mucosa was demonstrated.

When the drug is a water-soluble high molecular weight salmon calcitonin, plasma levels of salmon calcitonin in rabbits that were sprayed with a pharmaceutical preparation having a low osmotic pressure of 10 mOsm (Composition No. 23) to the nasal mucosa were markedly higher than those in rabbits that were sprayed with a pharmaceutical preparation having an almost isotonic osmotic pressure of 340 mOsm (Composition Nos. 25) or with a pharmaceutical preparation having a high osmotic pressure of 4000 mOsm (Composition No. 26), and, as shown in Table 5, the bioavailability is increased by 13 to 19 fold.

Even for the pharmaceutical preparations having a low osmotic pressure, plasma levels were almost equal to the pharmaceutical preparations having isotonic or high osmotic pressure when they do not contain a water-insoluble or water-low soluble substance (Composition Nos. 27 and 28).

These results indicate that the effect of osmotic pressure of the pharmaceutical preparation which is isotonic or lower on the permeability of the water-low soluble substance to the blood at the mucosa is markedly exhibited only when a water-insoluble or water-low soluble substance is included, and thereby the effect of the aqueous pharmaceutical composition of the present

invention for application to the mucosa was demonstrated.

With regard to the result that compares the absorptivity of fluorescein in Example 1 and Comparative example 1, the relationship between the osmotic pressure and bioavailability is shown in Figure 1. Also, with regard to the result that compares the absorptivity of 5-carboxy fluorescein in Example 2 and Comparative example 2, the relationship between the osmotic pressure and bioavailability is shown in Figure 2. Also, with regard to the result that compares the absorptivity of salmon calcitonin in Example 3 and Comparative example 3, the relationship between the osmotic pressure and bioavailability is shown in Figure 3. It is apparent that in any of the drugs, bioavailability increases with decreased osmotic pressure and that a water-insoluble and/or water-low soluble substance represented by crystalline cellulose carmellose sodium is required to obtain a high bioavailability.

Figure 4 is a photograph that shows the expansion of the composition when the composition of the present invention having an osmotic pressure of 10 mOsm and that having an osmotic pressure of 290 mOsm (isotonic) were added to the physiological saline having the same osmotic pressure as the mucus on the mucosa (thus, simulating mucus). The figure shows that the composition of the present invention having a low osmotic pressure remain at the addition site whereas the isotonic compositions easily disperse.

Example 4.

Fluorescein composition Nos. 29 to 33 for application to the mucosa comprising the components described in the following Table 7 were prepared. For each pharmaceutical preparation, osmotic pressure was measured using the Micro-Osmometer Model 3MO from Advance Instruments, Inc. The result is shown in Table 7. Bioavailability (B.A.) of the composition Nos. 29 to 33 determined by the method described in Working example 1

is also shown in Table 7. 120 minutes after this, blood was drawn from the rabbits, the nasal cavity was washed with 500 ml of 4 mM NaOH solution in water, and then the concentration of fluorescein in the wash solution was determined by HPLC. The amount of fluorescein in the wash solution relative to the amount given was calculated as a residual ratio in the nasal cavity, and the mean residual ratio in the nasal cavity for three rabbits is shown in Table 7.

Table 7

Composition No.	Composition	Osmotic pressure (mOsm)	residual ratio in nasal cavity (%)	B.A. (%)
29	Fluorescein: 0.1% w/w Carbazochrome: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w	5	49	30
30	Fluorescein: 0.1% w/w Carbazochrome: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Sodium chloride: 0.08% w/w	30	32	22
31	Fluorescein: 0.1% w/w Carbazochrome: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Sodium chloride: 0.2% w/w	72	10	10
32	Fluorescein: 0.1% w/w Carbazochrome: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Sodium chloride: 0.4% w/w	128	9	7
33	Fluorescein: 0.1% w/w Tranexamic acid: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w	7	51	28

Comparative example 4.

Fluorescein composition Nos. 34 to 38 for application to the mucosa comprising the components described in the following Table 8 were prepared. For each pharmaceutical preparation, osmotic pressure was measured using the Micro-Osmometer Model 3MO from Advance

Instruments, Inc. Bioavailability (B.A.) and the residual ratio in the nasal cavity of the composition Nos. 34 to 38 determined by the method described in Working example 4 are also shown in Table 8.

Table 8

Composition No.	Composition	Osmotic pressure (mOsm)	residual ratio in nasal cavity (%)	B.A. (%)
34	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w	5	23	63
35	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Sodium chloride: 0.08% w/w	30	15	47
36	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Sodium chloride: 0.2% w/w	72	5	16
37	Fluorescein: 0.1% w/w Crystalline cellulose carmellose sodium: 1.7% w/w Polysorbate 80: 0.1% w/w Benzalkonium chloride: 0.03% w/w Sodium chloride: 0.4% w/w	128	4	13

The residual ratio in the nasal cavity and retentivity in the nasal mucosa of the model drug fluorescein are higher by 2 to 3-fold in the Examples of the present invention (composition Nos. 29 to 33) containing a hemostatic agent (carbazochrome or tranexamic acid) than the in the Comparative examples (composition Nos. 34 to 37) containing no hemostatic

agent. In particular, when osmotic pressure is as low as 5 mOsm (composition No. 29) or 7 mOsm (composition No. 33), residual ratio in the nasal cavity is very high at about 50%. The result indicates that a drug, that permeates into the blood after a single administration of the drug, stays at the mucosa without permeating into the blood when coadministered with a hemostatic agent, and thereby the usefulness of the present invention has been shown for the drugs of which efficacy depends on the amount of the drug and on the time of retention at the local mucosa which may lead to side effects. Furthermore, it has been shown that the amount remaining in the mucosa is greater for the pharmaceutical preparations having low osmotic pressure for which the amount permeated to the blood is greater, and therefore the usefulness of the present invention becomes even greater when the pharmaceutical preparation has a low osmotic pressure.

Industrial Applicability

Thus, the first aspect of the present invention provides a composition for application to the mucosa which has efficient and high permeability of the drug through the mucosa to the blood. By using such a composition of the present invention for application to the mucosa, effects equal to or greater than those obtained with the conventional compositions can be obtained even at smaller doses or smaller administration frequencies than the conventional methods. This can lead to reduction in side effects.

The second aspect of the present invention provides a composition for application to the mucosa which has efficient and high permeability to the blood and retentivity at the mucosa. By using such a composition of the present invention for application to the mucosa, effects equal to or greater than those obtained with the conventional compositions can be obtained even at smaller

doses or lower administration frequencies than the conventional methods. This can lead to reduction in side effects.

Thus, the present invention extremely useful in terms of therapeutic and economic effects for drug therapies that employ application to the mucosa.

CLAIMS

1. An aqueous pharmaceutical composition for application to the mucosa, comprising one or more water-insoluble and/or water-low soluble substance, and one or more medicament, and having an osmotic pressure of less than 290 mOsm.

2. A pharmaceutical composition for application to the mucosa, comprising one or more hemostatic agent and one or more medicament.

3. An aqueous pharmaceutical composition for application to the mucosa, comprising one or more hemostatic agent, one or more water-insoluble and/or water-low soluble substance, and one or more medicament, and having an osmotic pressure of less than 290 mOsm.

4. The pharmaceutical composition for application to the mucosa according to claim 1 or 3, wherein said osmotic pressure is 150 mOsm or less.

5. The pharmaceutical composition for application to the mucosa according to claim 1 or 3, wherein said osmotic pressure is 60 mOsm or less.

6. The pharmaceutical composition for application to the mucosa according to claim 1 or 3, wherein said osmotic pressure is 30 mOsm or less.

7. The pharmaceutical composition for application to the mucosa according to claim 1 or 3, wherein said osmotic pressure is 10 mOsm or less.

8. The pharmaceutical composition for application to the mucosa according to claim 1 or any of claims 3 to 7, further comprising an osmotic pressure-controlling agent.

9. The pharmaceutical composition for application to the mucosa according to claim 8, wherein said osmotic pressure-controlling agent is a salt.

10. The pharmaceutical composition for application to the mucosa according to claim 9, wherein said osmotic pressure-controlling agent is sodium chloride.

11. The pharmaceutical composition for application

to the mucosa according to claim 8, wherein said osmotic pressure-controlling agent is a water-soluble sugar.

12. The pharmaceutical composition for application to the mucosa according to claim 11, wherein said osmotic pressure-controlling agent is glucose.

13. The pharmaceutical composition for application to the mucosa according to claim 1 or any of claims 3 to 12, wherein said water-insoluble and/or water-low soluble substance is a cellulose.

14. The pharmaceutical composition for application to the mucosa according to claim 13, wherein said cellulose is crystalline cellulose.

15. The pharmaceutical composition for application to the mucosa according to claim 1 or any of claims 3 to 12, wherein said one or more water-insoluble and/or water-low soluble substance is present as solid particles in an aqueous medium.

16. The pharmaceutical composition for application to the mucosa according to claim 1 or any of claims 3 to 12, wherein said one or more water-insoluble and/or water-low soluble substance is dispersed as solid particles in an aqueous medium.

17. (Amended) The pharmaceutical composition for application to the mucosa according to any of claims 1 or 3 to 16, further comprising a water-soluble polymer substance.

18. The pharmaceutical composition for application to the mucosa according to claim 17, wherein said water-soluble polymer is one or more selected from the group consisting of alginic acid, polyethylene glycol, glycerin, polyoxyethylene polyoxypropylene glycol, propylene glycol, pectin, low methoxyl pectin, guar gum, gum arabic, carrageenan, methyl cellulose, carboxymethyl cellulose sodium, xanthan gum, hydroxypropyl cellulose, and hydroxypropyl methyl cellulose.

19. The pharmaceutical composition for application to the mucosa according to claim 18, wherein said water-

soluble polymer is carboxymethyl cellulose sodium.

20. The pharmaceutical composition for application to the mucosa according to claim 18, wherein said water-soluble polymer is xanthan gum.

21. The pharmaceutical composition for application to the mucosa according to claim 18, wherein said water-soluble polymer is hydroxypropyl methyl cellulose.

22. The pharmaceutical composition for application to the mucosa according to claim 17, wherein the combination of said water-insoluble substance and water-soluble polymer is crystalline cellulose carmellose sodium.

23. (Amended) The pharmaceutical composition for application to the mucosa according to any of claims 1 or 3 to 22, further comprising a surfactant.

24. The pharmaceutical composition for application to the mucosa according to claim 23, wherein said surfactant is polysorbate 80.

25. (Amended) The pharmaceutical composition for application to the mucosa according to any of claims 1 or 3 to 24, wherein said medicament is a water-soluble medicament.

26. (Amended) The pharmaceutical composition for application to the mucosa according to any of claims 1 or 3 to 24, wherein said medicament is a liposoluble medicament.

27. (Amended) The pharmaceutical composition for application to the mucosa according to any of claims 1 or 3 to 26, wherein said mucosa is nasal mucosa.

28. (Amended) The pharmaceutical composition for application to the mucosa according to any of claims 3 to 27, wherein said hemostatic agent is one or more selected from the group consisting of tranexamic acid, epsilon aminocaproic acid, carbazochrome, carbazochrome sulfonate, carbazochrome sodium sulfonate, phytonadione, etamsylate, monoethanol amine oleate, thrombin, hemocoaglase, and adrenochrome monoaminoguanidine mesilate.

29. (Amended) The pharmaceutical composition for application to the mucosa according to any of claims 3 to 28, wherein the agent other than said hemostatic agent is one or more

selected from the group consisting of an antiallergic agent, an antihistamic agent, an anticholinergic agent, a steroid, a vaccine, and a substance for gene therapy, and the mucosa is nasal mucosa.

30. The pharmaceutical composition for application to nasal mucosa according to claim 29, wherein the agent other than said hemostatic agent is a steroid.

ABSTRACT

The present invention provides a pharmaceutical composition for application to the mucosa to be used in drug therapy comprising a water-insoluble and/or water-low soluble substance, a medicament, and an aqueous medium, and having an osmotic pressure of less than 290 mOsm. This composition is superior over conventional pharmaceutical compositions for application to the mucosa, due to efficient and high permeability to the blood at the mucosa. The present invention further provides a pharmaceutical composition for application to the mucosa comprising a hemostatic agent and a medicament. This composition is superior over conventional pharmaceutical compositions for application to the mucosa, due to permeability and retentivity at the mucosa.

Fig.1

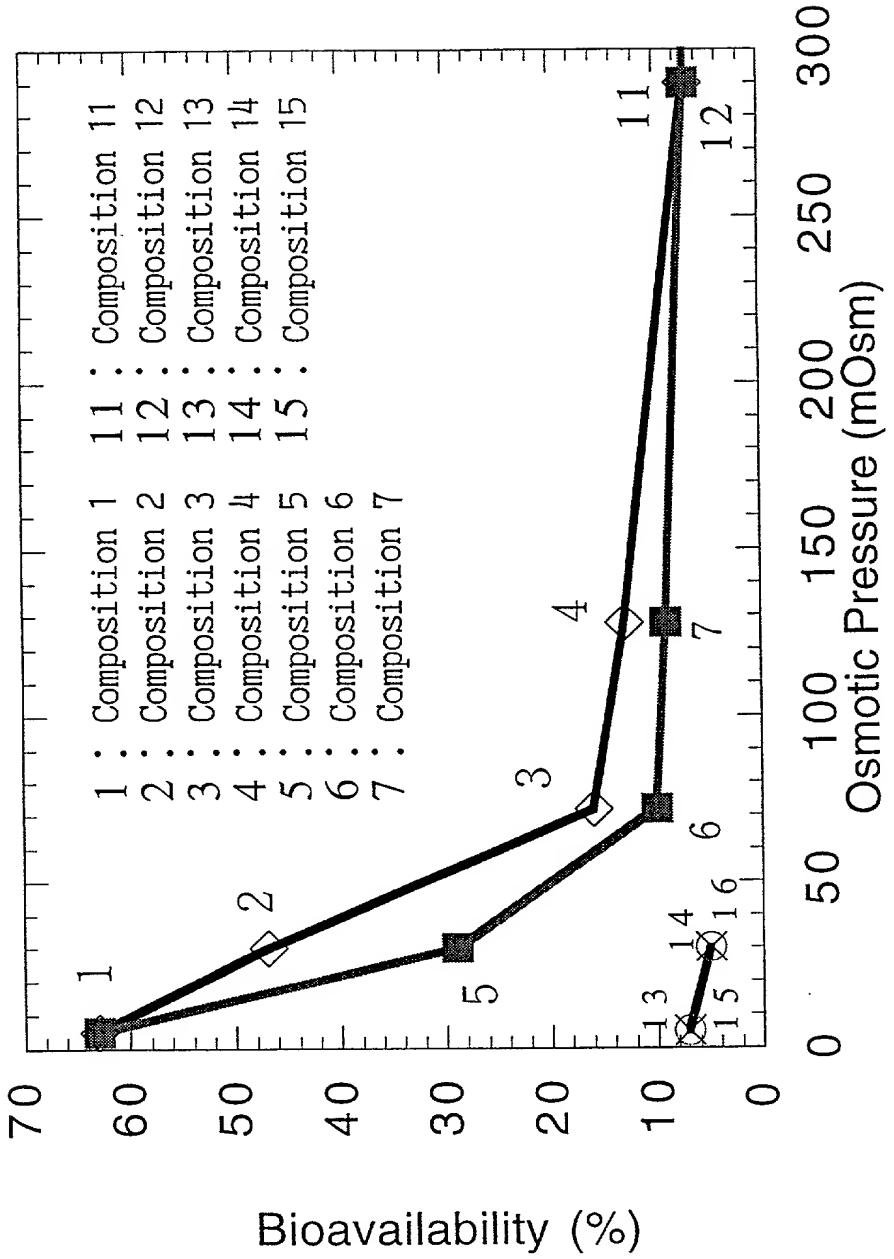
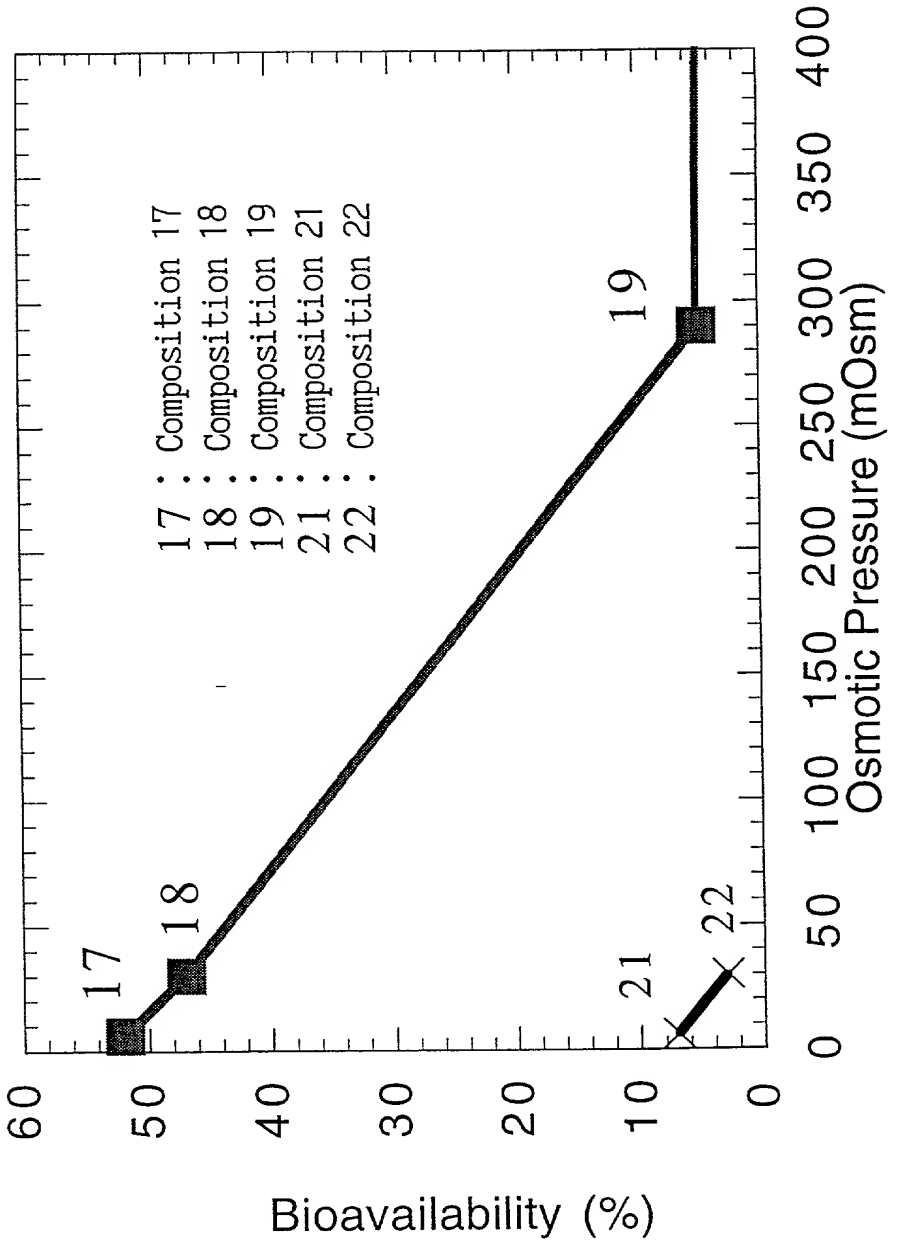


Fig.2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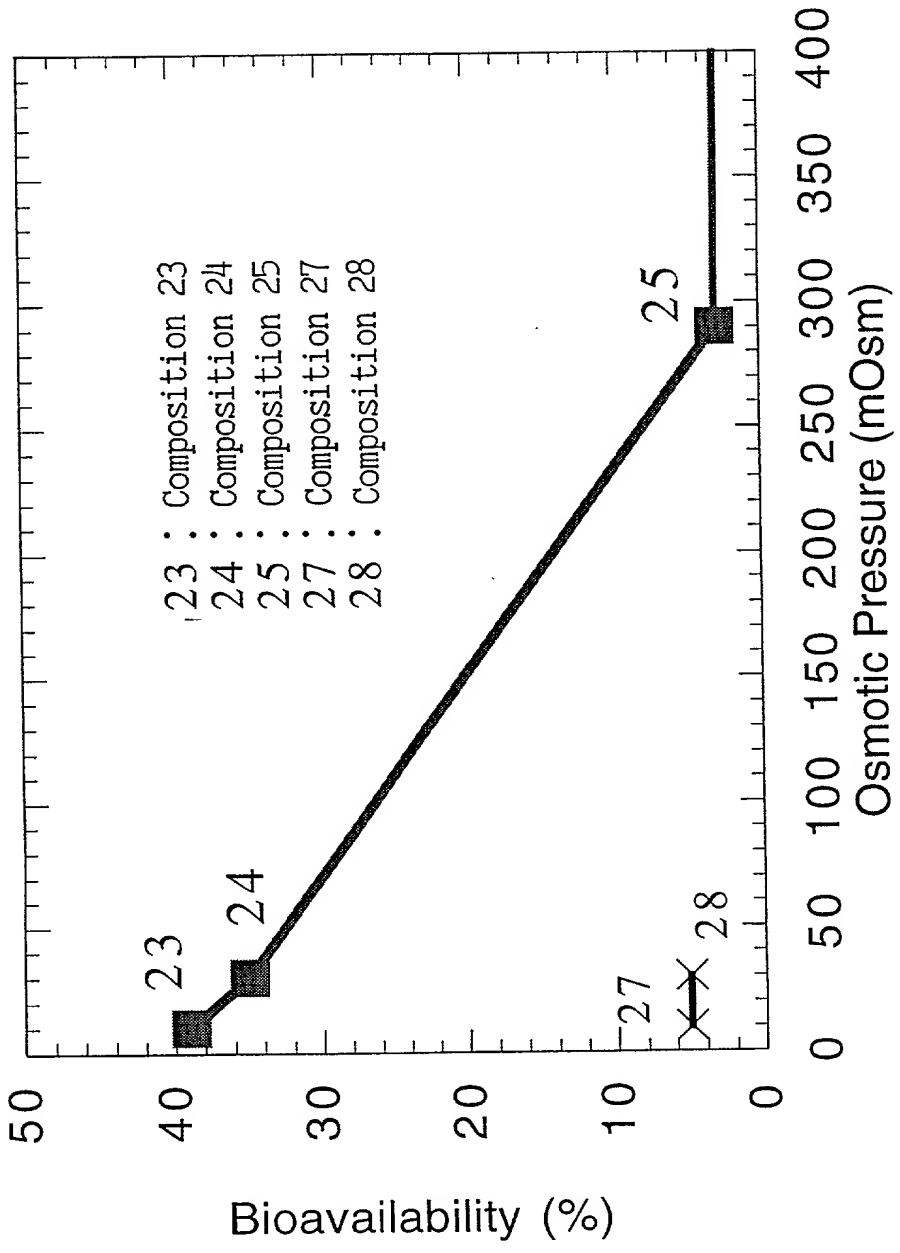
Bioavailability (%)
Osmotic Pressure (mOsm)

Fig. 3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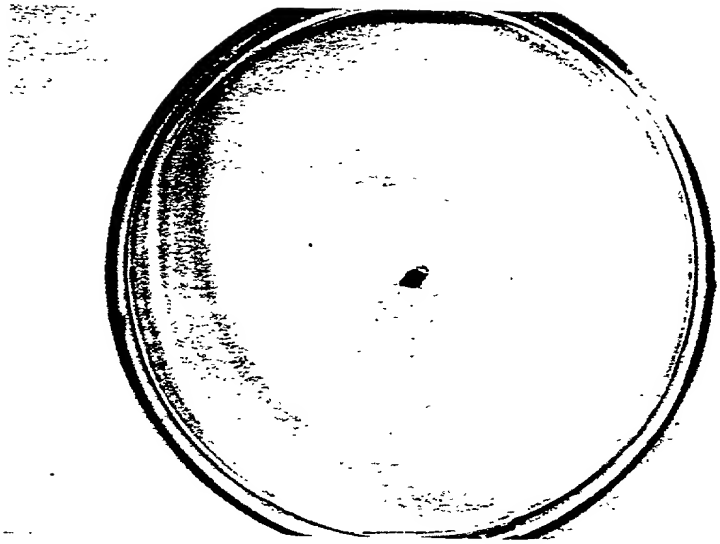
Bioavailability (%)
Osmotic Pressure (mOsm)

Fig.4

(A)



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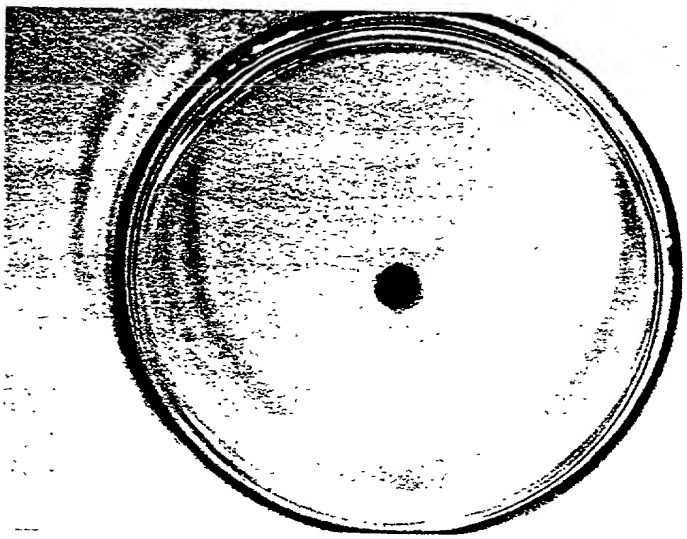

Declaration and Power of Attorney for Patent Application

特許出願宣言書及び委任状

Japanese Language Declaration

日本語宣言書

下記の氏名の発明者として、私は以下の通り宣言します。

As a below named inventor, I hereby declare that:

私の住所、私書箱、国籍は下記の私の氏名の後に記載された通りです。

My residence, post office address and citizenship are as stated next to my name,

下記の名称の発明に関して請求範囲に記載され、特許出願している発明内容について、私が最初かつ唯一の発明者（下記の氏名が一つの場合）もしくは最初かつ共同発明者であると（下記の名称が複数の場合）信じています。

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Pharmaceutical Composition for Application to Mucosa

上記発明の明細書（下記の欄でX印がついていない場合は、本書に添付）は、

the specification of which is attached hereto unless the following box is checked:

☐ ___月___日に提出され、米国出願番号または特許協定条約

国際出願番号を _____ とし、

（該当する場合）_____ に訂正されました。

☐ was filed on April 21, 1999
as United States Application Number or
PCT International Application Number

PCT/JP99/02126 and was amended on

September 28, 1999 (if applicable).
(under PCT Article 19)

私は、特許請求範囲を含む上記訂正後の明細書を検討し、内容を理解していることをここに表明します。

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

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私は、米国法典第35編第119条(a)-(d)項又は第365条(b)項に基き下記の、米国以外の国の少なくとも一カ国を指定している特許協力条約第365条(a)項に基づく国際出願、又は外国での特許出願もしくは発明者証の出願についての外国優先権をここに主張するとともに、優先権を主張している本出願の前に出願された特許または発明者証の外国出願を以下に、枠内をマークすることで、示しています。

I hereby claim foreign priority under Title 35, United States Code, Section 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Applications 外国での先行出願			Priority Not Claimed 優先権主張なし
10-110887(Pat.Appln.) (Number) (番号)	Japan (Country) (国名)	21/April/1998 (Day/Month/Year Filed) (出願年月日)	☐
10-110888(Pat.Appln.) (Number) (番号)	Japan (Country) (国名)	21/April/1998 (Day/Month/Year Filed) (出願年月日)	☐
(Number) (番号)	(Country) (国名)	(Day/Month/Year Filed) (出願年月日)	☐

私は、第35編米国法典119条(e)項に基づいて下記の米国特許出願規定に記載された権利をここに主張致します。

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

(Application No.) (出願番号)	(Filing Date) (出願日)	(Application No.) (出願番号)	(Filing Date) (出願日)

私は、下記の米国法典第35編第120条に基づいて下記の米国特許出願に記載された権利、又は米国を指定している特許協力条約第365条(c)に基づく権利をここに主張します。又、本出願の各請求範囲の内容が米国法典第35編第112条第1項又は特許協力条約で規定された方法で先行する米国特許出願に開示されていない限り、その先行米国出願書提出日以降で本出願書の日本国内又は特許協力条約国際出願提出日までの期間中に入手された、連邦規則法典第37編第1条第56項で定義された特許資格の有無に関する重要な情報について開示義務があることを認識しています。

I hereby claim the benefit of Title 35, United States Code Section 120 of any United States application(s), or 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code Section 112, I acknowledge the duty to disclose any material information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: Patented, Pending, Abandoned) (現況: 特許許可済、係属中、放棄済)
(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: Patented, Pending, Abandoned) (現況: 特許許可済、係属中、放棄済)

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Japanese Language Declaration

(日本語宣言書)

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POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith (*list name and registration number*)

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Japanese Language Declaration
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